

Selective Serotonin Reuptake Inhibitors (SSRIs)

Summary

- Selective serotonin reuptake inhibitors (SSRIs), as the class name indicates, act primarily by inhibiting the reuptake of serotonin by the serotonin transporter, thereby increasing the synaptic concentration of serotonin that remains available to bind to postsynaptic receptors.
- SSRIs are comparable to other antidepressants in efficacy, but are markedly safer and better tolerated than first-generation antidepressants (e.g., tricyclic antidepressants, monoamine oxidase inhibitors); consequently, they are preferred for the treatment of numerous psychiatric disorders, including major depression and anxiety disorders. [\[49961\]](#)[\[58403\]](#)[\[58404\]](#)[\[50542\]](#)[\[50550\]](#)[\[49959\]](#)[\[62891\]](#)
- SSRIs differ from each other with respect to their degree of selectivity for the serotonin transporter; however, this has not translated into clinical superiority of any SSRI.
- The choice of agent is dependent upon factors such as drug interactions, previous patient response, drug-specific precautions, and efficacy for the specific condition being treated. [\[50534\]](#)
- SSRIs, with the exception of paroxetine, have been associated with a modest but statistically significant increase in the QTc interval. The maximum recommended dose of citalopram was reduced to reflect the dose-related risk of QT prolongation and torsade de pointes associated with the drug. The product labels have various recommendations regarding use of SSRIs in patients with long QT syndrome, risk factors for QT prolongation, or coadministration with other drugs that cause QT prolongation. [\[28269\]](#)[\[59321\]](#)
- Escitalopram is the least likely of the SSRIs to be subject to clinically significant metabolic (CYP450 system) drug-drug interactions.
- Paroxetine is the only SSRI with strong warnings regarding pregnancy risks; epidemiological studies have shown that paroxetine use during pregnancy is associated with an increased risk of congenital malformations, particularly cardiovascular malformations. [\[28260\]](#)[\[46229\]](#)[\[62732\]](#)
- Based on available data, paroxetine and sertraline may be the preferred SSRIs to use in females who are breast-feeding. [\[45642\]](#)[\[46229\]](#)[\[61269\]](#)[\[62732\]](#)

Pharmacology

SSRIs inhibit the reuptake of serotonin by serotonin transporters located on presynaptic neurons, resulting in increased synaptic availability of serotonin at postsynaptic receptors. Therefore, the therapeutic action is presumed to result from presynaptic and postsynaptic adaptive mechanisms secondary to reuptake inhibition, and it evolves over several weeks to months of treatment. The desensitization of 5-HT_{1A} autoreceptors in the dorsal raphe nucleus is one potentially important mechanism. The drug agents in the SSRI class do differ in their degree of selectivity for binding to the serotonin transporter (escitalopram > citalopram > sertraline > fluvoxamine > paroxetine > fluoxetine) and their potency of serotonin reuptake inhibition (paroxetine > sertraline > escitalopram > fluoxetine > citalopram > fluvoxamine), but these factors have not been proven to lead to clinically relevant differences in efficacy.[\[50533\]](#)[\[50589\]](#)[\[50591\]](#)[\[50542\]](#)

SSRIs do not have a significant affinity for histaminergic, alpha-1 adrenergic, postsynaptic dopamine, GABA, or glutamate receptors nor do they inhibit monoamine oxidase (MAO). The receptor binding activity of SSRIs results in a more favorable safety and adverse event profile compared with first-generation antidepressants such as tricyclics and monoamine oxidase inhibitors. Paroxetine is the only SSRI with clinically relevant anticholinergic effects. These effects may be additive with other anticholinergic medications in any patient, but geriatric adults may be more susceptible to the anticholinergic effects of the drug than younger adults.[\[64280\]](#)[\[63923\]](#)

Comparative Efficacy

- A meta-analysis of all head-to-head clinical trials of SSRIs showed very few significant differences between agents in treatment response (50% or greater reduction in symptoms as measured by a change from baseline in score on a validated instrument); however, greater efficacy was demonstrated by escitalopram and sertraline compared with fluoxetine or paroxetine.[\[50533\]](#)
- In this same meta-analysis, escitalopram and sertraline also had the best overall acceptability profile (measured by all-cause discontinuation rates).[\[50533\]](#)

Drug Interactions

MAO inhibitors

SSRIs are contraindicated in patients receiving MAO inhibitors or within 2 weeks of their discontinuation. Medications with MAOI activity, such as linezolid or intravenous methylene blue, are also contraindicated for use with SSRIs because of an increased risk of serotonin syndrome.[\[28260\]](#)[\[28269\]](#)[\[28270\]](#)[\[28343\]](#)[\[32127\]](#)[\[44058\]](#)[\[43998\]](#)[\[43999\]](#)[\[50507\]](#)

SSRIs, SNRIs, and other serotonergic drugs

Any use of an SSRI with other serotonergic agents increases the likelihood of serotonergic adverse effects and should be monitored closely. Drugs that have serotonergic properties include opiates, triptans, most antidepressants, amphetamines, St. John's wort, tramadol, lithium, buspirone, and others.[\[28260\]](#)[\[28269\]](#)[\[28270\]](#)[\[28343\]](#)[\[32127\]](#)[\[44058\]](#)[\[43998\]](#)[\[43999\]](#)[\[50507\]](#)

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Drugs that prolong the QT interval

prolonging effects.[\[28260\]](#)[\[28269\]](#)[\[28270\]](#)[\[28343\]](#)[\[32127\]](#)[\[44058\]](#)[\[43998\]](#)[\[43999\]](#)[\[50507\]](#)[\[59321\]](#)

Drugs that are metabolized by CYP450 isozymes

elevate escitalopram concentrations.[28260][28269][28270][28343][32127][44058][43998][43999][50507][50595]

Appendix A

Therapeutic Use Table

Indications	Citalopram Hydrobromide	Escitalopram	Fluoxetine Hydrochloride	Fluvoxamine Maleate	Paroxetine Hydrochloride	Paroxetine Mesylate	Sertraline Hydrochloride
Renal Impairment	Yes	Yes			Yes	Yes	
Dosing Adjustment							
Hepatic Impairment	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dosing Adjustment							
depression	Yes	Yes	Yes	Yes †	Yes	Yes	Yes
generalized anxiety disorder (GAD)		Yes	Yes †	Yes †	Yes	Yes	Yes †
hot flashes	Yes †		Yes †		Yes	Yes	Yes †
obsessive-compulsive disorder (OCD)	Yes †		Yes	Yes	Yes	Yes	Yes
panic disorder	Yes †	Yes †	Yes	Yes †	Yes	Yes	Yes
posttraumatic stress disorder (PTSD)	Yes †		Yes †	Yes †	Yes	Yes	Yes
premature ejaculation			Yes †		Yes †	Yes †	Yes †
premenstrual dysphoric disorder (PMDD)	Yes †		Yes	Yes †	Yes	Yes	Yes
social phobia (social anxiety disorder)	Yes †	Yes †	Yes †	Yes †	Yes	Yes	Yes

Yes – Labeled

Yes † – Off-label

Appendix B

Top 20 Adverse Reactions / Side Effects Table

Adverse Reaction / Side Effect	Citalopram Hydrobromide	Escitalopram	Fluoxetine Hydrochloride	Fluvoxamine Maleate	Paroxetine Hydrochloride	Paroxetine Mesylate	Sertraline Hydrochloride
anxiety	4%	Reported	6 - 15%	5 - 8%	2 - 5%	2 - 5%	Reported
diarrhea	8%	8%	8 - 18%	11 - 18%	6 - 18%	6 - 18%	20%
dizziness	>2%	5%	9%	11 - 15%	6 - 14%	6 - 14%	12%
drowsiness	18%	6 - 13%	5 - 17%	22 - 27%	9 - 24%	9 - 24%	11%
dyspepsia	5%	3%	6 - 10%	8 - 10%	2 - 5%	2 - 5%	8%
ejaculation dysfunction	6.1%	12%	2 - 7%	8 - 11%	13 - 28%	13 - 28%	3 - 8%
hyperhidrosis	11%	4 - 5%	2 - 8%	6 - 7%	6 - 11%	6 - 11%	7%
insomnia	15%	9 - 12%	10 - 33%	21 - 35%	8 - 24%	8 - 24%	20%
libido decrease	1.3 - 3.8%	3 - 6%	1 - 11%	4 - 6%	3 - 12%	3 - 12%	4 - 7%
nausea	21%	15 - 18%	12 - 29%	34 - 40%	4.3 - 26%	4.3 - 26%	26%
tremor	8%	Reported	3 - 13%	5 - 8%	4 - 11%	4 - 11%	9%
xerostomia	20%	6 - 9%	4 - 12%	10 - 14%	3 - 18%	3 - 18%	14%
yawning	2%	2%	1 - 11%	2 - 5%	4 - 5%	4 - 5%	<2%
asthenia	Reported	Reported	7 - 21%	14 - 26%	12 - 22%	12 - 22%	
constipation		3 - 5%	5%	4 - 10%	5 - 16%	5 - 16%	6%
fatigue	5%	5 - 8%		Reported	<4.9%	<4.9%	12%
headache		24%	21%	22 - 35%	6.3 - 27%	6.3 - 27%	Reported
impotence (erectile dysfunction)		2%	1 - 7%	2%	4 - 10%	4 - 10%	4%
anorexia	4%		4 - 17%	6 - 14%	1 - 9%	1 - 9%	
pharyngitis			3 - 10%	6%	1 - 4%	1 - 4%	

Appendix C

Safety Issues Table

Safety Issue	Citalopram Hydrobromide	Escitalopram	Fluoxetine Hydrochloride	Fluvoxamine Maleate	Paroxetine Hydrochloride	Paroxetine Mesylate	Sertraline Hydrochloride
REMS							
MedGuide	Yes	Yes	Yes	Yes	Yes	Yes	Yes
children	BBW	BBW	BBW	BBW	BBW	BBW	BBW
citalopram hypersensitivity	X	X					
escitalopram hypersensitivity	X	X					
MAOI therapy	X	X	X	X	X	X	X
pregnancy					X	X	
suicidal ideation	BBW	BBW	BBW	BBW	BBW	BBW	BBW

X – Contraindicated

X-BBW – Contraindicated and Black Box Warning

BBW – Black Box Warning, Not Contraindicated

Yes – REMS or MedGuide is available